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Testing regimes in clinical trials: Evidence from four polio vaccine trajectories

Ohid Yaqub

Abstract:

This paper highlights distinctive features of a neglected class of economic activity in the domain of medical innovation, namely the creation of testing regimes in clinical trials, asking how their nature might be expected to affect innovation of medical technology. It argues firstly that clinical trials are not simply about passively validating an already well-known technology and verifying its safety. Rather, clinical trials are part of a more active process of learning that allows pharmaceutical innovations to be useful outside the laboratory. It argues secondly that product development can proceed along a number of long and costly paths before a product's behaviour in actual practice becomes clear, which can make selecting between alternative courses of action difficult. Thus, product choice and product development need to go hand-in-hand. To consider these arguments, the paper maps out four trajectories of polio vaccine development, tracing their paths through clinical trials since the 1950s, and describes some of the defining features of testing regimes for medical innovation. These include institutions that integrate knowledge and co-ordinate skills in testing processes, and capabilities for allocating testing resources, managing testability constraints, sharing knowledge and improving commensurability between testing communities.

1 Vaccine innovation and research translation: What are the needed institutions?

Epidemics periodically emerge as policy priorities, prompting calls for new vaccines (for example avian influenza, HIV, Ebola). Policy discussion often focuses on how firms can be given exemptions from regulatory barriers so that candidates can be rushed through clinical trials and certified for the market, especially when framed as international emergencies. This assumes a rather limited role for the range of institutions engaged in medical innovation outside of the laboratory, wherein clinical trials might even be seen as a mere regulatory hurdle that is imposed on firms before certifying products as being safe for the market. Vaccine innovation is often characterised as a process where research is not only translated into a product, but it is one that can be accelerated if only the social validation and bureaucracy of clinical trials can be streamlined.

The purpose of this paper is to draw attention to a neglected area of innovation study, namely the creation of testing regimes in clinical trials, asking how their nature might be expected to affect innovation of vaccines and perhaps also other medical technologies such as pharmaceutical drugs and devices. The paper describes some of the defining features of testing regimes by drawing together ideas from studies of innovation, evolutionary economics, and sociology of science and technology. Pharmaceuticals are becoming increasingly difficult to develop (Hopkins et al. 2007; Scannell et al 2012; Gittleman 2016). They exhibit high levels of attrition and few candidates make it to the costlier clinical phases (Arrowsmith 2013). The few that do make it to clinical trials are seen as candidates that await confirmation of whether or not they are safe and effective. This understates the extent to which many of these candidates are unfinished products when they reach clinical trials and undergo considerable further development in a testing regime in order to *become* safe and effective. This paper shows that testing regimes are expensive to set up and maintain, and entail the creation of both physical and non-physical ‘knowledge’ infrastructure.

The paper makes two claims. First, clinical trials (i.e. testing that takes place in humans) are not simply about passively validating an already well-known technology and verifying its safety. Rather, clinical trials are part of a more active process of learning that allows pharmaceutical innovations to be useful outside the laboratory. Vaccines provide an extreme context to test this claim. Unlike most other medical technology vaccines are usually intended for people who are already healthy, which heightens concern for safety. There is special concern for product development to take place well in advance of clinical phases.

Yet, even in vaccine innovation where safety is the paramount regulatory and social concern – to many it is the only concern (see Yaqub et al 2014) – we shall see that the search for efficacy extends well into the clinical phases and how, over the course of the vaccine’s ‘career’ (Blume 1992; Hopkins 2006), the learning process becomes more governance intensive in the clinical phases (for a direct comparison to learning in pre-clinical stages, see Yaqub and Nightingale 2012). If science does not lead to a clear and costless path to technology then, even in a case like vaccines, there is a need to understand what else is needed for product development, and what activities are going on under the banner of clinical trials and regulation.

Second, within a vaccine’s career, multiple trajectories can be pursued (Dosi 1982; von Tunzelmann et al. 2008; Rip 2012). Although possible trajectories may become apparent by learning in laboratories and animals, the overall performance characteristics of the different trajectories operating in different systems will not have been revealed in their entirety. Product development can proceed along a number of long and costly paths before a product’s behaviour in actual practice becomes clear, which can make selecting between alternative courses of action difficult.¹ Thus, product choice and product development need to go hand-in-hand.

The paper will substantiate these two claims through historical case study. Below, I develop a framework for analysing the case study by defining salient features of testing regimes. The paper contributes directly to a stream of literature concerning the evolution of medical knowledge (Gelijns and Rosenberg 1994; Mina, et al. 2007; Rosenberg 2009; Nelson et al 2011; Consoli et al 2016). It also draws on history of technology and engineering studies literature concerning the accumulation of technological knowledge (Layton 1974; Constant 1980; Vincenti 1990, Rosenberg and Steinmueller 2013), and specific work indicating that the rate and direction of vaccine innovation is influenced by the ability to set up ‘testing regimes’ and test repeatedly (Nelson 2008; Yaqub 2010; Yaqub and Nightingale 2012). The intuition here is that all complex technologies share a protracted process of development, be they vaccines or turbojets.²

¹ The costs of achieving greater clarity about alternatives can be significant: ‘Development expenditures accounted for approximately 67% of total R&D spending. These figures, at the very least, suggest great skepticism about the view that the state of scientific knowledge at any time illuminates a wide range of alternative techniques from which the firm may make cost-less, off-the-shelf selections’ (Rosenberg 1994:13). Rosenberg identified this, choosing between alternatives, as being ‘what economic analysis is all about’.

² However, as mentioned already and as will be explored empirically, an important characteristic that distinguishes medical technology from other complex technology is that safety considerations permeate this process in its entirety.

2 Testability, trajectories and infrastructure: a framework for analysis

Technologists test ideas with instruments and skill under varying conditions, according to shared standards, and with the active participation of co-ordinating institutions. I refer to this triad of elements (conditions, instruments, and institutions) as a testing regime. We will see in the empirical section how the resulting *testability* of trajectories can differ with significant social consequences (in terms of the characteristics of the vaccines we end up with and the infrastructure organised around them).

Testing regimes do not proceed aimlessly, they require a ‘social vision’ set out by technical and practitioner communities as well as broader communities (Blume 1992:64-70). This is because technologies have a purpose that is not completely inherent to their physical properties (Polanyi 1958:328). Purpose and function combine to form ideas for operational principles (how a technology works) (Vincenti 1990:209), and social visions are formed around which operational principles can accelerate and develop as a trajectory within a vaccine’s career, often in plurality because theory is a weak guide to practice (Blume 1992; Yaqub 2010).³

Testing of operational principles proceeds through experimental stepping-stones, by building up understanding in simplified animal models before more realistic testing is undertaken in humans (Yaqub and Nightingale 2012). Testing conditions are therefore controlled to trade-off ease of learning (simplicity) against clinical relevance (complexity). Instrumentalities (Price 1984a, 1984b) – interpreted in this paper as physical devices, equipment and instruments, together with the skills to use them⁴ – allow testing conditions to be adjusted.

Technological practice draws on science in specific and limited ways that centre on the creation of testing conditions. Instrumentalities can benefit learning processes in two opposing ‘directions of fit’ (Nightingale 2014:5-8). In learning for science, instrumentalities help to control conditions which are not often repeated or replicated⁵ but need to be highly simplified for identifying patterns and causal explanations (Hacking 1983; Deutsch 1997). In learning for technology, instrumentalities help to control

³ A more explicit insight into how social visions interact with technological developments can be found in the relationship between diagnosis (Rosenberg 2002), diagnostic instruments and the establishment of disease causation (pathology) (see Yaqub 2010). Before vaccine development efforts can take flight, there are some critical elements – namely, a disease and an associated pathogen, and a diagnosis capable of characterising both reliably.

⁴ These skills include the development of routines, heuristics, techniques, know-how (as opposed to only know-what), highly specific practices and procedures, experience of what tends to work and what does not (Nelson and Winter 1982; Pavitt 1999).

⁵ Scientists rarely replicate or repeat experiments, they more often seek to improve and set precedents (Hull 1988).

conditions, where causal explanations are less important⁶, but creating new effects and ways of replicating them reliably in more complex environments becomes prime. Such perspectives can be applied to medical innovation, where clinical knowledge is argued to be significantly independent from advances in scientific understanding; this has been referred to as an important ‘point of discontinuity with the traditional literature on health technology diffusion’ (Consoli and Ramlogan 2012:315).

Two styles of testing can be used when manipulating testing conditions (Yaqub and Nightingale 2012). Passive ‘testing as validation’ involves testing whether similar problems have similar solutions. This can be largely non-theoretical because it is not necessary to know how a technology works in order to know that it does work (Nightingale 2004:1271). However, it offers little guidance about what to do if tests fail. In such cases, rather than a cycle of conjecture and refutation, active ‘testing as experimental intervention’ is used to build artificial experimental conditions that create new phenomena to allow theoretical learning (Hacking 1983).

Since new effects are being created, local variations in practice and instruments can make establishing their reliability difficult: conditions or standards between tests may be too different to be able to observe empirical regularities; accuracy and relevance of observations may be checked with different instruments. More importantly, it can mean that comparison with other effects (new or otherwise) is not possible. With low comparability, the interpretation of testing data in order to eliminate less suitable trajectories becomes subject to intense social negotiation as interests form around particular trajectories. In the case study, we will see how governance structures can either co-ordinate various activities and instruments to increase comparability across conditions or it can provide leadership that mediates arguments about how the instruments are calibrated and the criteria for success or failure.

Co-ordination between research and development groups is needed in the form of ‘invisible infrastructure’⁷ in order to ensure the new knowledge arising from testing processes is accumulated. In the case study, we will see how biomarkers - correlates of immunity - help guide the direction of trajectories (Eichler et al. 2008:819). These allow developers to turn subjective qualitative desires into objective quantitative specifications and design goals that can be tested for in progressively less simplified conditions (Vincenti 1988). We will also see the development of knowledge indexes or taxonomies where, for example, disease symptoms can be categorised or immune responses can be ranked. This

⁶ ‘Technology can exist as an autonomous body of knowledge because it is *possible to know how to produce effects without knowing how those effects are produced*’ (Nightingale 2004:1271, original emphasis).

⁷ Building on Nightingale’s (2004) use of the term, it refers to non-tangible infrastructure needed for knowledge accumulation.

allows for agreement and shared judgement to form over technical feasibility in learning and testing processes. Such examples of ‘invisible infrastructure’ have important public good characteristics for the activity of multiple research groups and do not develop autonomously alongside technological opportunities. They are a shared utility, created at high fixed cost, and need governance to set up and maintain.

This process can offer multiple options for product development, but they do not necessarily remain open permanently. As technical systems themselves undergo change, certain options can become harder to develop, or can even be locked out altogether (David 1985; Stirling 2008; Rip 2012). So, certain choices cannot be made too early before products are sufficiently developed and before the option is conceivable, nor can they be made too late when the surrounding infrastructure no longer viably supports the option.

To illustrate these features of knowledge accumulation are present even in the clinical trial stages of product development, I follow Blume’s (2005) and Chataway et al.’s (2010) approach of illustrative case studies in vaccine innovation. My research design takes the historical career of poliomyelitis vaccine as its empirical focus. To increase within-case validity I use four trajectories, one of which is counter-theoretical where a key element in the theory (supporting technical infrastructure) is absent and the nascent trajectory no longer remains a viable option. The history has been reconstructed on the basis of data that draws on a range of documentary sources, including practitioners’ accounts, scientific reviews and journals, biographies, policy reports, newspaper articles, and publications by NGOs such as advocacy groups, charities and foundations. The data was collected as part of a large multi-year study on vaccine innovation (Yaqub 2010). Taken in isolation, many of these sources purport to document the actions of great men and famed organisations (like like Jonas Salk and the March of Dimes). However, a theoretically-informed secondary synthesis reveals a knowledge accumulation process at work that persists beyond the heroism of a single agent or organisation, spanning multiple actors and organisations.

3 Mapping technological trajectories in polio vaccine development

3.1 Context for clinical polio vaccine development

When Landsteiner and Popper showed poliomyelitis was spread by an infectious agent in 1908, and when Franklin Roosevelt was struck by poliomyelitis in 1921, the development of a social vision for a vaccine was set in motion (Yaqub and Nightingale 2012). After fatal testing failures in the 1930s, a new testing regime was developed in 1947: new testing conditions provided by a plentiful and steady supply of

monkeys; new instrumentalities such as tissue-culturing techniques that tightened feedback loops for experimental learning, and new institutional efforts included a co-ordinated large-scale poliovirus typing project (Yaqub and Nightingale 2012).

By 1953, poliomyelitis afflicted more than 20 per 100,000 in the US (Robbins 2004:17). Emphasis shifted to creating testing conditions in humans and transitioning to clinical vaccine development. Tom Rivers, who headed the research committee in the National Foundation for Infantile Paralysis, put out a call, “It is time that we got ready to go somewhere, and somebody ought to come up with some concrete experiments that will be done in human beings on a small scale in order to get going” (Carter 1965:126).

With the chances of making a poliomyelitis vaccine much improved, and an urgent social imperative, a number of groups worked with different operational principles that were to become the bases for different technological trajectories. Hammon chose to pursue a passive immunisation approach, whilst Salk and Sabin successfully pursued active immunisation approaches.⁸

3.2 Passive immunisation: Testing for design and field-based capabilities

As noted in theory, a critical part of the vaccine design process can be described as a difficult and uncertain transformation of qualitative goals into objective ones. I begin by outlining the feasibility of passive immunisation as an operational principle, before analysing considerations made about vaccine design and organisational capabilities during the move to human testing.

As an operational principle, Hammon believed that γ -globulin, an antibody obtained from pooled plasma with known neutralising activity in the laboratory, might offer benefits in practice. Rather than prevent poliovirus infection, his immediate goal was to prevent disease on the nervous system caused by the infection (Carter 1965; Paul 1971; Plotkin and Vidor 2004). Permanent immunity through repeated infection might be achieved, but without the symptoms of poliomyelitis. The idea carried weight in part because passive administration of serum achieved some success against measles virus (MRC 1948).

In 1948 Morgan and Bodian were able to protect monkeys from one type of poliomyelitis (Carter 1965:64; Paul 1971:405). By using graded doses of virus, which produced varying levels of antibody, they produced different degrees of immunity in monkeys. This represented an improvement in invisible infrastructure because antibody experiments conducted by different research groups could be compared to

⁸ Passive immunisation refers to the transfer of virus-specific antibodies. Active immunisation refers to the transfer of an altered form of the virus that induces virus-specific antibodies.

a shared index of immunity in monkeys. Researchers knew how much antibody would create weak immunity in monkeys (against small doses of virus) and how much antibody would create strong immunity (against high doses of virus). Hammon wanted to develop a similar index for humans so that one could make a safe start to ascertaining ‘how much was enough for humans?’ and ‘how long do they last in the blood?’.

The Foundation created a ‘Committee on Immunization’ to manage strategic and logistic aspects of human vaccine trials (Carter 1965:125; Paul 1971:407). It was a daring role given the traumatic failures of the Brodie-Kolmer trials two decades earlier, where the deaths - testing as validation - did not offer much guidance about how to proceed (Yaquib and Nightingale 2012). Fear about using killed or live virus was a common theme, but Hammon’s vaccine did not contain any virus, only γ -globulin, a form of ‘ready-made’ antibody.

Hammon’s preliminary field trial showed that relatively low levels of antibody could prevent invasion of the central nervous system (Hammon et al. 1953). The results provided vaccine developers pursuing different trajectories, such as Salk and Sabin, not only with the confidence that disease could be prevented, but also a tangible performance criterion. The subjective aim of immunity had become an objective goal of putting antibodies in the blood. By helping to ascertain how much antibody was needed to prevent infection, Hammon effectively provided a correlate of immunity, a biomarker. The testing regime had a bar, against which potential designs could be compared.

Questions of how quickly immunity could be established in the blood, and how long it would last for in the blood under various conditions remained. Hammon argued that with his γ -globulin, ‘its effect would be immediate and would represent no danger to any child’ (Hammon 1950:702). The mention of ‘no danger’ was a deliberate attempt to highlight that other vaccine trajectories were contemplating the inclusion of virus, whereas his did not. And whilst his vaccine did indeed serve immunity quickly, it was suspected to not last as long as antibodies produced by the body through active immunisation as proposed by the other trajectories. Hammon also argued the active immunisation trajectories needed multiple injections to establish their longer lasting immunity. Although passive immunisation might not need multiple injections, Hammon apparently overlooked the fact that his subsequent clinical trial would deplete reserves of γ -globulin.⁹ A further trial with more people - and hence more varied testing conditions - was needed to address these issues of speed, durability and quality of immunity.¹⁰

⁹ The limited availability of γ -globulin restricted its use. Obtaining γ -globulin was an expensive and time consuming process and depended on voluntary blood donations. At the same time, the Korean War and hospital needs were

The Foundation funded Hortsman (1952) and Bodian (1952) to see if passive immunisation protected monkeys from very high, lethal doses of poliovirus of all three strains. Compared to Morgan's experiment in 1948, these testing conditions were more technologically relevant (because they involved all three strains at high doses), and perhaps even scientifically less interesting (because the theoretical concept of neutralising antibodies had already been established). The protection achieved under these conditions convinced the panel to fund a pilot study of 5000 children. Panel members realised that this size would not yield statistically significant results, rather the study's purpose was 'to gain experience in organisation and administration, as well as to evaluate the public's and medical profession's reaction to such a trial' (Rinaldo 2005:793).

The details of the trial which needed to be organised were very broad.¹¹ Most critical was 'the definition of the severity of the paralytic disease, for which they used a carefully graded scale of muscle function loss' (Rinaldo 2005:793). Similar to the virus typing project, and the antibody index, this is another example where the Foundation set up invisible infrastructure to compare future observations to a set of known conditions, thereby ensuring that those observations would contribute to the cumulative growth of technological knowledge. It might otherwise have been seen as a chore, with little, if any, scientific merit.

The pilot results were encouraging and public support was very strong, with hundreds of volunteers being turned away by day four (Hammon et al. 1953). Problems included such issues as lack of access to autoclaves to sterilise the needles. A larger trial was quickly approved, which involved 55,000 children. The result of this trial was considered, 'conclusive evidence of a very significant reduction in the total number of cases of paralytic poliomyelitis' (Hammon et al. 1953:758).

The trajectory lost momentum as the Foundation turned its attention to Salk's and Sabin's vaccine candidates, perhaps taking the depletion of the γ -globulin as a serious impediment, or perhaps it was

drawing on supplies. O'Connor warned that there was not enough to provide 'even temporary protection to the 46 million children and adolescents most susceptible to poliomyelitis' (Rinaldo 2005:795). Nevertheless, the Foundation spent \$7m boosting γ -globulin production and a further million children were protected in the poliovirus season of 1953 (Rinaldo 2005).

¹⁰ The Immunization Committee initially turned down Hammon's request for a larger scale controlled trial (Rinaldo 2005). They wanted to see more animal and human data before embarking on a complicated and expensive clinical trial (the trial ultimately cost the Foundation \$1m). They were also concerned about using placebo controls, which had never been used before, and its moral and social acceptability (Rinaldo 2005).

¹¹ They included how to: blind the vaccine vials, select a type of control inoculum, source and set dosage of γ -globulin, types of syringes, packaging, venue, injection administration site on the body, consider legal aspects such as written informed consent, select geographical areas undergoing epidemics of a suitable magnitude, gain approval by local population, manage publicity and preparation of clinics, and follow up studies to identify incidence cases.

hoped the other trajectories would provide longer-lasting and stronger protection. Note that the efforts of an earlier, awkward, quasi-failure trajectory can end up enabling subsequent more successful trajectories, in this case, through active governance to ensure shared learning. Hammon concluded that, ‘perhaps the greatest contribution of the γ -globulin trials... demonstrated that a very low concentration of antibodies will protect man’ (Hammon et al. 1953:1283). Aside from taking this design standard from monkeys and establishing a correlate of immunity in human conditions, a graded scale of paralytic disease was also developed with which to evaluate other trajectories – crucial invisible infrastructure.

The trials were seized as an opportunity for the Foundation to build up organisational capabilities in acquiring local knowledge for testing outside laboratory conditions, and co-ordinating people, resources, logistics and public support. Alongside the accumulation of technological knowledge, the Foundation had begun setting up the infrastructure for moving potentially more dangerous vaccines to trial in humans, and for comparing between different trajectories.

3.3 Killed vaccines: Testing regimes for taking ‘calculated risk’

This section discusses how a more risky vaccine was tested in humans despite the fact that the product being tested was considered unfinished and still under development - tests were designed not only to learn and improve on the product, but also to allow comparison between trajectories on a number of dimensions of performance, not least that of safety. This vaccine’s operational principle would be more risky than Hammon’s because it contained killed virus (rather than mere antibodies), but less risky than using live vaccine. There was no test to make certain all the vaccine’s virus was killed, so the decision to test in humans was a difficult one - the initial risk appears to have been borne by certain sections of society. As with Hammon, we will see efforts by Salk to lock in the trajectory, but we will also see the mechanisms put in place to mediate differences in opinion and maintain comparability between trajectories.

By 1953, Salk had shown that poliovirus could be inactivated by formaldehyde, providing the basis for his operational principle and trajectory of development (Salk 1953). Moreover, he determined how much formalin affected inactivation, and conducted safety and immunogenicity studies in animals (Benison 1967; Robbins 2004). If there was any doubt as to whether Salk’s animal findings could be transferred to children, Howe’s (1952) paper made it clear, entitled ‘Antibody response of chimpanzees and human beings to formalin inactivated trivalent poliomyelitis vaccine’.¹² Salk, too, had started preliminary studies

¹² Howe tested six children at the Rosewood school, whom he noted as, ‘low-grade idiots or imbeciles’ (1952:265), and was able to report that ‘both children and chimpanzees develop readily demonstrable neutralising antibodies at

in humans which showed that antibodies could be increased to relatively high titres in children already infected at the Watson Home for Crippled Children.¹³ But these advances, aside from any modern-day ethical testing concerns, were leading to a somewhat problematic vaccine.

Conventional wisdom held that a live-attenuated vaccine could confer longer-lasting immunity because it more closely mimicked a true infection (Carter 1965; Klein 1976; Smith 1990). Several of the Committee's senior virologists, such as Albert Sabin and the Nobel Laureate John Enders, questioned the relevance of short-lived antibodies and doubted the safety of a vaccine prepared from virulent poliovirus, regardless of how thoroughly it was inactivated, especially after the failed vaccines of the 1930s (ibid). Enders is even quoted as having confronted Salk and calling his work, "quackery" (Carter 1965:88). But for Salk, the notion that only natural infection or a vaccine made of living pathogen could offer durable protection was nonsense. Governance structures were needed to increase comparability with the passive and live vaccine trajectories, and to provide leadership on what counts as success criteria.

Members of the Foundation acknowledged 'sharp differences' in the Immunization Committee and tried to manage them (Paul 1971:407). For example, regarding concerns about whether an inactivated poliomyelitis vaccine really was inactivated, Rivers said at a Committee meeting, "I think we will all admit that there is no *test* to be sure the stuff is inactive. Why not just accept that? Why kid ourselves? Why use the word inactive? Why not just say, 'safe for *use*?' It won't produce disease, and that's all there is to it" (Carter 1965:126, my italics).

Such 'nervous brawling' stalled any kind of progress (Carter 1965:129). So, in 1953, the Foundation set up a new and smaller committee because, as Weaver is quoted as saying, "The immunization committee was not able to function with the necessary dispatch. It could get entangled for months in technical debates. Furthermore, its members were virologists and the decisions on which we needed help were not exclusively virological. The Vaccine Advisory Committee with experienced public health men... was a far more efficient group" (Carter 1965:176; Paul 1971:411). The need for a second committee suggests that the design of tests is not an entirely objective and technical matter, and includes broader institutional considerations. It was also established in part to limit conflicts of interest that may arise from having competing designers playing the role of "architect, carpenter and building inspector" all at once (Weaver quoted in Carter 1965:179).

comparable levels following the injection of small quantities of clarified monkey cord suspensions containing formalin inactivated poliomyelitis virus' (1952:265).

¹³ Like Howe, Salk tested children who were not infected but were 'mentally retarded' and found that the levels of antibody production were equally encouraging (Chase 1982).

Salk recalls the arbitrary nature of deciding when and precisely what to test. “All we had were several dozen experimental preparations, some with adjuvant, some without, some containing one type of virus, some another or a third or all three, some made with monkey tissue, some with testes, some inactivated for ten days, some for thirteen, some for twenty one” (Carter 1965:130). Salk insisted, “I don’t know that we even have a vaccine yet. That term was used, but I think it should be understood that we are using it as a colloquial expression. We have preparations which have induced antibody formation in human subjects” (Carter 1965:152). The possible permutations of experimental conditions Salk describes seem endless. Salk was eventually pushed into readiness by the Foundation.¹⁴

Although Rivers thought the Salk vaccine was ‘something slightly better than γ -globulin, something by definition imperfectible,’ he felt it was ‘worth a try’ (Carter 1965:152). Harry Weaver wrote, ‘The practice of medicine is based on a calculated risk... If [we wait until more] research is carried out, large numbers will develop poliomyelitis who might have been prevented from doing so... our work must be governed by scientific and sociological concerns’ (Carter 1965:147; Benison 1967).¹⁵ From these exchanges, it seems that vaccine development is not a process of optimisation. Vaccines are developed to function only sufficiently well enough to fulfil a social purpose. That purpose drove the Foundation to urgently begin planning for a major field trial.

In the design of the trial, the planned use of placebo controls was problematic, but the precedent seemed necessary. Initially, Weaver sought simplicity and economy, and suggested that the poliomyelitis rate be compared between vaccinated and non-vaccinated school-children of the same age (Carter 1965:176). However, the Vaccine Advisory Committee suggested that socioeconomic differences between those who volunteered and those who did not would weaken the study.¹⁶

¹⁴ A member of the Vaccine Advisory Committee said, “Progress can be made even [when] we have so little knowledge... the time has come to really go at the inactivated material... The live virus is fine, but if you think about it as a public health measure, it is a difficult thing to use... I don’t think you have a good excuse morally to go into infectious material until we have shown that inactivated material was unsatisfactory” (Carter 1965:128).

¹⁵ The trade-off was emphasised in a telegram to convince sceptics, ‘It is said that to await certainty is to await eternity’ (Smith 1990:295).

¹⁶ A ‘good’ vaccine might go amiss. Less well-educated families living in poorer areas were less susceptible to poliomyelitis, tending to contract the non-paralytic form in infancy and gaining immunity. Moreover, they were less likely than high income, well-educated, families to submit their children to the trial. So, if the poliomyelitis rate in the vaccinated group ended up being similar to that among the unvaccinated, it might be because the trial only immunised the most susceptible children. *This was a testability constraint, and a different design-technique would be needed for the test to have the necessary resolving power to prove its efficacy.*

Salk felt that his vaccine was not up to such a stringent test, and lapses in the manufacturing process or unimpressive results of a double-blind test might scupper the opportunity to improve it (Carter 1965:178). I quote him at length in the paragraphs below to show that the design of the tests was at the centre of his concerns at the time, and that the parameters of the tests left an indelible mark on the nature and characteristics of the vaccine.

“The sensible thing, I thought, was to accept the urgencies of the situation and continue improving the vaccine. I thought the field trial should be designed to permit this, not prevent it... I thought we should concentrate on polio prevention and be less concerned about making epidemiological history with an elegant double-blind study. I was afraid that, for some people, the *kind* of test had become more important than the kind of protection the vaccine might be able to provide.”

“I wanted to know who had been vaccinated so that blood samples could be taken promptly. If tests then showed that a certain batch of vaccine was producing unsatisfactory results, the children could be revaccinated with better material. At the same time, we could be taking steps to improve the manufacturing process and avoid new batches of inferior vaccine. Finally I was uncomfortable about giving placebo shots to children, depriving them of immunity in what might turnout to be an epidemic year. Many public health officials agreed with me on this.”

“You had this rigid insistence that a ‘product’ be submitted forthwith for ceremonious testing. The emphasis on ‘product’ and on ritual and on looking good in the eyes of certain elements in the scientific community was being allowed to obscure the real purpose of everyone’s work, which was the prevention of polio” (Carter 1965:178).

The long quote illustrates Salk’s attempt to focus testing efforts on product development. He wanted clinical trials to accelerate only this trajectory, and limit direct comparison with other trajectories that had potential to be successful (namely that of Sabin’s). The Foundation needed to strike a balance between product development and product choice.

In order to address the concerns of parents, teachers, and such ‘humanitarians’ O’Connor announced that an observed control plan would be used, in which children would not be injected but only observed (Meldrum 1998). The Foundation asked health officers for advice and support, who suggested that the

Foundation may not be able to maintain impartiality in such evaluation (Meldrum 1998). So O'Connor appointed Thomas Francis to head the evaluation of the trials, a critical but unglamorous task, based on 'his deft direction of complex field trials of influenza virus vaccines during World War II' (Markel 2005:1408). However, Francis would not accept until he manoeuvred between health officers, paediatricians, clinical poliomyelitis specialists, statisticians and virologists to engineer a change in the trial design to include placebos (Meldrum 1998).

Addressing concerns about volunteer recruitment in the placebo plan, the evaluation group decided that it could rely on the widespread fear of the disease; members agreed that 'it would not be difficult to sell as there is a high attack rate... [and] there would still be a 50% chance of a child receiving the vaccine' (Meldrum 1998:1235). Francis compromised with Salk and others to a certain extent with observed design in some areas, but his insistence on the placebo plans in other areas was particularly important in the context of the vociferous criticisms from Enders, Sabin and others about the validity of the killed-vaccine concept.¹⁷

The trial for the vaccine went ahead in 1954 and was the largest of its kind to be run. It was not a cheap gamble, grants for the field trial and its evaluation cost the Foundation a total of \$7.5m. The results of nearly 2 million children were presented on 12th April 1955, and the vaccine was found to be safe and 70% effective, with breakthrough cases judged to be less severe (Smith 1990).¹⁸ With financial guarantees from the Foundation, industrial production facilities were already built and ready to operate (Blume and Geesink 2000). The Foundation paid a further \$7.5m to the manufacturers for 10 million Salk vaccine doses (Chase 1982). The products of six producers were licensed within days and poliomyelitis cases dropped from 58,000 in 1952 to 5,600 in 1957.

Paul, whose career in poliovirus research spanned both eras, contrasts the 1935 and 1955 vaccines, products of testing as validation and testing as experimental intervention respectively. 'The situations were in no way comparable, for the Brodie-Kolmer vaccines had been launched in the face of colossal ignorance, whereas the Salk-type vaccine had been promoted under circumstances which from the start almost guaranteed success. And yet one cannot help feeling a twinge of sympathy for the two figures of 1935 who were so alone in the midst of their disgrace, in contrast to the powerful forces of the National Foundation, the US Public Health Service, and innumerable advisory committees that stood back of the

¹⁷ The placebo plans were also part of the Foundation's effort to legitimise an institution governed by non-experts. It was important given the possible conflict of interest arising from the Foundation evaluating a vaccine they, as an organisation, developed and sponsored.

¹⁸ Cases where volunteers are diagnosed with poliomyelitis despite being vaccinated in the trial.

Salk type vaccine’ (1971:420). Paul notes how different the testing regimes were and how the difference was critical for knowledge to accumulate.

3.4 Live vaccines: testing in the shadow of the killed vaccine

This section reviews how improvements to the testing regime enabled the establishment of live vaccine trajectory. It emphasises the historical-dependency of such trajectories by highlighting the role of non-fiscal testing resources, and ultimately describes different decisions taken by public health authorities in the USSR and USA. Because the virus is live, the lack of a safety test becomes a major issue of testability.

As he had done with the yellow fever virus, Max Theiler achieved attenuation by repeatedly infecting the brains of living mice with poliovirus until the virus no longer caused paralysis (but still retained its capacity to stimulate an immune response) (Chase 1982). He reported it to the Foundation in 1946, which then funded further research to see if poliovirus could also lose its ability to infect the central nervous system – which it did on repeated passage through non-nervous system tissues – to make this trajectory safer to pursue as an operational principle (Robbins 2004).

The live attenuated poliomyelitis vaccine approach was feasible only after certain developments in the testing regime because the approach relied on striking a balance between efficacy and safety (Yaquib and Nightingale 2012). This entailed searching for virus that is not pathogenic (disease causing) but retains some of its virulence (ability to infect). The development of tissue culture techniques¹⁹ facilitated the rapid emergence of variation in strains, whilst the availability of monkey models allowed vaccine developers to select for pathogenicity and virulence traits²⁰, and the typing project allowed putative vaccine preparations to be challenged without added confusion.

¹⁹ Viral culture techniques were significantly improved by Dulbecco and Vogt (1954). Adapting techniques for growing bacteria, they grew virus in microscopically thin mono-layers of chick embryo tissue cells. The colonies proliferating from the growth of a single viral particle could be identified, counted and isolated. This made it easier to purify specific lines of virus, which was extremely valuable for those looking to prepare a live vaccine (Paul 1971:406; Robbins 2004:19).

²⁰ Selecting strains with monkeys meant that live vaccine development did not need to rely on few and imprecise in-vitro markers of virulence, such as growth at higher temperature (Paul 1971:458). Instead, a more authoritative test for neurovirulence, adopted as the standard by the regulatory agencies, was devised where monkeys had to be inoculated through their central nervous system (Robbins 2004:20). Incidentally, establishing this as the authoritative test for neurovirulence was another example of important *invisible infrastructure*.

Sabin was one of several groups²¹ working in this way (Paul 1971; Robbins 2004). The Foundation provided him with \$1.2m between 1953 and 1961, and \$2m in total (Carter 1965:357; Chase 1982:303). In 1955, Sabin began a trial on inmates in Chillicothe Federal Prison in Ohio (Carter 1965:357; Smith 1990:301). His vaccine was successful, but the Foundation saw little reason to take chances with a larger scale trial of an infectious live vaccine when Salk's field trial had demonstrated efficacy the previous year. Large-scale trials of Sabin's vaccine, and those of others, would be difficult to interpret because the Salk vaccine had been licensed and was being used widely.²²

There is clearly a path-dependency element to testing processes in vaccines (see also Blume 2005), but I would like to draw attention to a slightly different view. In the early experiments, poliomyelitis researchers faced a shortage of virus; Evans and Green, who were beaten to the Nobel Prize, faced shortage of human embryonic tissue; Hammon faced issues with a shortage of γ -globulin; whilst Sabin faced a shortage of people to test on. These cases represent a scarcity of testing resources. These resources are not fiscal, as is commonly emphasised in health and vaccine development literature (see for example, Lanjouw 2003; Archibugi and Bizzarri 2004; Barder 2005), but can be anything from the availability of monkeys, γ -globulin, primary isolates, to simply people as test subjects. They were unlikely to have been resolved by market failure approaches or policies that focussed on pecuniary issues alone; they require institutional co-ordination.

The theory section also highlighted how the design of tests can be inherently constrained; such testability constraints can significantly impair the development of a trajectory, which, in this case, was testing for safety. The safety concerns in this trajectory extended beyond simply whether the virus in the vaccine was sufficiently attenuated to prevent it from causing disease. The major concern centred on its genetic stability and whether the live-attenuated virus would *remain* safely attenuated as it replicated. One of the advantages of the live vaccine was that after it passed through the intestines and was excreted by the vaccinee, it might then go on to confer immunity to someone else in the community. But the same advantage became a disadvantage for those who thought that, after several passages through community members, the altered vaccine strain might undergo progressive genetic changes such that it reaches a degree of virulence comparable to that of wild-type polioviruses. The success of the entire live approach

²¹ Other groups were led by Hilary Koprowski at the Wistar Institute, Herald Cox at Lederle Laboratories, and Joseph Melnick at Yale, all of whom tested their prototype live vaccines on institutionalised children (Chase 1982).

²² For example, when, in 1959, Herald Cox had the opportunity to test his live vaccine in Florida, Sabin dismissed any excitement by pointing out that too many people had taken Salk vaccine for the test to mean anything (Carter 1965:365).

therefore turned on proving that any cases of poliomyelitis was not caused by the vaccine reverting back to virulence after replication in the host.

Melnick found that live vaccine virus passaged through children was sometimes virulent enough to paralyze monkeys (Carter 1965:381). This caused concern, but there was no way in which a test could show that a given case of poliomyelitis in humans had been caused by the live vaccine, even if the victim was struck by poliomyelitis shortly after taking a live vaccine. If virus recovered from the victim resembled the wild type, one could suppose that it had taken over the intestines, and driven away the vaccine virus, before causing the disease (wild type-induced disease). Alternatively, one could decide that the vaccine virus had changed to resemble the wild type and become virulent, thereby causing vaccine-induced disease. Either way, testing primary isolates would not be able to prove a vaccine guilty.

This was a serious testability constraint for this trajectory, it made designing a test for measuring live vaccine safety virtually impossible, never mind one that could be compared to the safety of a killed vaccine. In the absence of a test that could offer commensurable assurances of safety, the live vaccine continued to be perceived as being more risky. Closely tied with these perceptions were the assumptions of the vaccine designers, about the social context in which their designs would be used. Safety would become more readily observable as a systemic and subjective feature, as protagonists argued risks and benefits in different contexts.

Due to the testability constraint surrounding safety, and the prior use of Salk's vaccine, Sabin was forced to look abroad to conduct large-scale trials. In 1958, 200,000 children in a Singapore trial received Sabin's live vaccine in an effort to curtail their epidemic (Paul 1971:454). By 1960, approximately 100 million people in the former USSR and Eastern European countries had received the vaccine. By the end of the year enough evidence had been established to secure licensure in the US for Sabin's live vaccine (Paul 1971:456).

However, the continued existence of distinct trajectories depended on variation in health systems because a given vaccine-attribute could serve as a merit in one and as a drawback in another. As a Soviet public health official remarked, "Our inoculation program was a public-health measure, not a field trial. It was designed to suit our medical services. In attempting to inoculate a population the size of ours, could there be any serious confusion about whether to give away candy drops, when the alternative was injection requiring so much more apparatus and personnel? Our work with the Sabin vaccine must be viewed in terms of public health and not as a strictly controlled scientific experiment" (Carter 1965:359). Here, the

broader vaccine system and operational context comes into view as being decisive for the viability of a trajectory.

If the Sabin vaccine could actually be shown to cause paralytic poliomyelitis, the finding would have been more significant for the US than for the Soviet Union. The Soviet Union was suffering poliomyelitis incidence rates of 94 per million (Carter 1965:363), much higher than that of the US, so any vaccine that could reduce that figure faster (because it could confer immunity to the non-vaccinated too) would be allowed the deficiency of a few vaccine-caused cases. It only represented one dimension in a broader set of criteria for the health system as a whole.

The protagonists of each vaccine promoted their interests and preferred choice, but the way in which a vaccine's attributes complemented existing infrastructure and health systems is likely to have had a greater influence in determining their adoption.²³ The ensuing history of the changing relative merits and drawbacks of the Salk and Sabin vaccines has been astutely discussed elsewhere (Blume and Geesink 2000; Blume and Lindner 2004; Blume 2005). It is worth noting, however, that as incidence of poliomyelitis decreased in the US over the next thirty years, the perception of risks and benefits changed and so the choice of vaccine changed too.²⁴ In the next section, we turn our attention to vaccines' technical systems and infrastructure, and how they affect continued vaccine innovation.

3.5 The changing importance of thermostability in polio vaccines

The development of a more thermostable poliomyelitis vaccine was made a high priority in 1991 by the Children's Vaccine Initiative (CVI). The need for a thermostable vaccine emerged from the high-profile effort to eradicate poliomyelitis but the trajectory was stymied by the way the surrounding technological systems and infrastructure of immunisation evolved. A large proportion of the total cost and effort of

²³ Cox was benefiting from an aggressive publicity campaign by Lederle touting its advantage of a single dose vaccine that still protected against all three strains (trivalent) (Carter 1965:365). Koprowski managed to trial his vaccine in 9 million people but had his vaccine turned down by the US government because it caused some lesions in monkeys (Paul 1971:454). Salk argued that his vaccine was effective and that they needed to wait longer, without introducing other vaccines, to see definitive results of an imperfect vaccination program. And Sabin's appeared to be the newer more modern vaccine with which the public health service could have a second chance of executing a vaccination program of more complete coverage (Carter 1965:372). Sabin's field trials in the Soviet Union were so effective they were doubted, and it took a report by Hortsman, who was dispatched there by the WHO, to verify the standards and evidence (Paul 1971:455; Robbins 2004:20).

²⁴ 'The conclusion [of a comparative analysis of live and killed vaccine] is heavily dependent on assumptions of risk of exposure to wild virus in the US. Major declines in risk of exposure... could alter the balance significantly' (Hinman, Koplan et al. 1988:295). Despite the high costs of switching from live to killed vaccine, the Advisory Committee on Immunisation Practices recommended the change in 1996 and US vaccine policy delivered killed vaccine exclusively from 2000 onwards (Plotkin and Vidor 2004:1484).

immunisation programmes relate to the creation and maintenance of a cold chain to ensure that vaccines are kept in conditions where they can retain their potency until the point of final delivery.²⁵ The cold chain system had to be geared up to cope with the least stable vaccine, which in the early 1990s was Sabin's poliomyelitis vaccine (Lemon and Milstien 1994).

As the movement towards poliomyelitis eradication gathered momentum, a 'mopping up' strategy was needed that relied on house-to-house administration of the vaccine to those at highest risk of poliomyelitis (Aylward et al. 2003). Eliminating the last 5% of cases has proved to be difficult because they often extended beyond the reach of the cold chain network and infrastructure. Workers' mobility could be sharply increased in those hardest-to-reach areas if a thermostable vaccine could be developed, one that could be carried 'in the pockets' of workers for several days.

To co-ordinate development efforts between a number of universities, vaccine institutes and commercial firms, a Product Development Group was established in the CVI (Lemon and Milstien 1994). Vaccine designers translated these qualitative attributes into quantitative goals, just as Hammon did when he demonstrated how much antibody was needed, just as Salk did when he showed how much inactivation was needed, and just as Sabin did when he showed how much attenuation was needed. The target was set to develop a vaccine that could withstand 37°C for 7 days, and retain a potency after such a thermal challenge of $<0.5 \log_{10}$ loss of titre of each of the 3 vaccine strains, with minimal change to viscosity (Milstien et al. 1997).

By 1995, a new operational principle of thermostability had been established.²⁶ But the principle was not developed further and the trajectory was aborted for three reasons. First, concern over scarcity of vaccine resources played a role in hindering the development, just as it had done for that of the Sabin and

²⁵ The costs include capital outlays on refrigeration equipment but also expenditure on maintenance such as, procuring adequate fuel, ensuring reliable power supply, undertaking repair and management of the systems, and educating users of the dangers of over-refrigeration and vaccine freezing. Freezing can occur if vaccines are placed too closely to the walls of ice-lined refrigerators, or embedded in ice-packs that have not been allowed to melt a little. Taken together, these issues represented 8% of the total costs of immunising a child in parts of the developing world (WHO-EPI 1992). Freeze sensitive vaccines constituted over 31% of the US\$439 million that UNICEF spent on all vaccines in 2005, and more than three quarters of all vaccine shipments were exposed to freezing temperatures at some point during distribution to health centres (Matthias, Robertson et al. 2007).

²⁶ Wu et al. (1995) showed that suspension of poliovirus in 87% deuterium oxide (D₂O, known as heavy water) results in a significant increase in the stability of the virus when incubated at 37°C 42°C or 45°C. As noted in theory, science and technological practice can be quite independent from each other. It was not understood exactly why stability is improved - a scientific question - but what made this an operational principle is that the stabilisation effect was recognised as being reliable, predictable and useful; all important technical attributes.

Hammon vaccines. There were controls on the movement of heavy water isotopes, which is an essential component in the preparation of nuclear weapons.

Second, developing a thermostable vaccine would not eliminate the need for cold chain systems because other essential vaccines would still need refrigeration. Improving the thermostability of a single vaccine would have had a negligible effect on reducing the overall cost of maintaining the cold chain infrastructure.

Third, a different technology, the development of vaccine vial monitors (VVM), inhibited the development of thermostable vaccines because VVMs can indicate thermal inactivation for each individual vial helping to ensure quality and safety of vaccine delivery in weak infrastructure settings (Zweig 2006). Indeed VVMs are being used for evaluating how effective cold chains are, locating weak links and breaks in the cold chain, and identifying incidences of vaccine freezing (Zweig 2006). So, VVMs serve to strengthen the cold chain paradigm by monitoring the stability of heat-labile vaccines, thereby making the development of a thermostable vaccine a lesser priority.

A thermostable polio vaccine was not an option that was easily available before 1950, before sufficient knowledge had been accumulated in clinical trials. But nor was the option easily available after 1991. Somewhere between 1950 and 1991, the window for an easily viable thermostable vaccine had opened and closed.

4 Discussion

The paper reiterates a call made nearly two decades ago to redress a ‘curious neglect’ of this process of knowledge accumulation through testing (Rosenberg 1994:14):

‘The extent to which total R&D spending is dominated by the Development component calls attention to critical aspects of the manner in which technological knowledge grows. It is the essence of these technologies that their designs need undergo protracted periods of testing, redesign and modification, and retesting before their performance characteristics are well enough understood for them to be produced and sold in reasonable confidence. Although these expensive and time consuming development activities are typically not of great interest for their specific scientific content, the information so acquired is absolutely essential from an economic point of view.

Performance characteristics of high-technology products simply cannot be accurately predicted without extensive testing... It cannot be emphasised enough that such information typically cannot be deduced from scientific principles.’ (Rosenberg 1994:14).

By 1950, some might have claimed that ‘the science was more or less there’.²⁷ In contrast, this paper has traced the considerable technological knowledge accumulation that was needed in clinical contexts (rather than in laboratories and monkeys) before effective poliomyelitis vaccines could emerge. Little about these efforts could be described as inevitable; the testing regime involved firstly the deliberate manipulation of testing conditions through active experimental intervention, secondly, the development of new instruments and techniques, and thirdly, institutions playing a co-ordinating role to ensure shared rather than fragmented learning.

4.1 Testing as experimental intervention

The paper showed how testing conditions were manipulated in carefully controlled ways. It may have seemed like Hammon initially pursued passive testing as validation, testing whether a similar problem (measles) had a similar solution (serum injection), but the Hammon trajectory then showed signs of active ‘testing as experimental intervention’ wherein conditions such as virus strains, viral doses, and the number of test subjects were all varied in the search for new effects and new theory. Throughout the process, safety shaped the approach. Indeed, the Hammon trajectory was pursued largely because it was a safe way of learning in humans, before turning to vaccine preparations containing virus.

The decision to trial vaccines containing virus was seen as a calculated risk to safety. There was no safety test to ensure that Salk’s vaccine was completely killed. Similarly, it was impossible to design a safety test to see whether the Sabin vaccine causes poliomyelitis. However, unlike Salk’s trajectory, learning in Sabin’s trajectory was unable to forge ahead by carefully manipulating testing conditions because of the limited number of remaining vaccine volunteers to test on in the US in the wake of the Salk trials. These two *testability* barriers eventually forced live-vaccine development abroad.

Testing in different countries revealed the more relative dimensions of the process. Eugenically-oriented medical ethics, which considered mentally and physically handicapped children and prisoners to be the

²⁷ Some might claim that ‘the science’ was in place even earlier after Flexner demonstrated that monkeys surviving poliomyelitis could resist re-infection in 1910. Indeed, Flexner claimed that a vaccine would be ready in six months.

subjects of choice for medical experimentation, provided realistic testing conditions and eased safety concerns. We may be free of that particular aspect of the 1950s, but we are still laden with the subjective nature of safety amongst the rich and poor. The different decisions taken by the American and Soviet public health authorities reflected their interpretations of safety as well as their health systems' requirements.

We should therefore expect questions about future vaccine trials to centre on the ethical safety of their design, on how closely the testing conditions resemble the final operating environment and how well the vaccine will fit into surrounding health systems. This cannot be done on the basis of scientific deductions alone. Predictability and reliability in vaccines are established through repeated but carefully managed testing processes by exposing the vaccine to increasing levels of complexity in localised contexts. The extent of localisation in testing processes can be seen in a recent example where vaccine developers trying to offer a vaccine against 'holiday stomach bugs' requested clinical trial volunteers fly out to a holiday destination in an effort to simulate holiday behaviours and environments (Laurence 2009).

4.2 Managing multiple vaccine trajectories

The paper tracked multiple trajectories of vaccine development that were pursued in sequence and in parallel. Important technological knowledge was accumulated sequentially through a series of trajectories: Hammon's trajectory supported other trajectories based on different operational principles (Salk and Sabin's active vaccines). It would be difficult to characterise the additional effort associated with the development of parallel trajectories as duplicated or wasted effort, particularly when the trajectories ended up offering their own distinct design advantages (and disadvantages) relative to different health systems. In fact, the paper shows that considerable institutional effort went into ensuring multiple paths of development remained open and comparable (see below on invisible infrastructure). Most of the vaccine designers tried to lock development efforts into their trajectory. The antagonism between the scientific orthodoxy, of which Sabin and Enders were part, and technological newcomers such as Salk and Weaver, might have mired all development efforts were it not for a mediating organisation.²⁸

²⁸ The patterns of institutional rewards and credit accorded to Salk and Sabin differed significantly suggesting that the pursuit of elegant science and urgent technology development are distinct endeavours with opposing 'directions of fit' (Nightingale 2014). Salk was a household name but his colleagues in the science community never afforded him the recognition and awards accrued to Sabin (Oshinsky 2005:270). 'Many attributed the professional discrimination against Salk to the flamboyant backing of O'Connor and the resultant media frenzies, which were offensive to 'pure scientists'' (Katz 2004:187). Although Salk received the Congressional Gold Medal and other

The Foundation established mechanisms for mediating differences of opinion about efficacy, safety and when to test. One principal means for doing this was to strengthen the test by insisting on an unprecedented placebo arm, against the wishes of Salk who described it as a ‘fetish of orthodoxy’. Despite Salk’s efforts to negotiate otherwise, the Foundation insisted on doing this to make the clinical trails comparable with other trajectories. The result was that growth of knowledge was shared and accumulated (rather than fragmented). Another means was to set up an alternative Vaccine Advisory Committee that included a mix of skilled public health officials, scientists and medics, rather than scientists alone. This retained the sense of urgency and social purpose at the core of the Foundation, again encouraging the pursuit of multiple trajectories (to effectively hedge bets).

4.3 Visible and invisible infrastructure

The paper showed that, in order to accumulate technological knowledge, institutions needed to develop both visible and invisible infrastructure. Invisible infrastructure included the concerted effort to ensure qualitative attributes were interpreted into a set of shared quantitative design targets for the development of operational principles, as shown in all four of the vaccine trajectories. Hammon provided the all-important ‘correlate for immunity’, showing that relatively little antibody was needed for efficacy. Salk demonstrated how much inactivation was needed and Sabin showed how much attenuation was needed. Later, tangible targets were set not only for thermostability, but also for temporal durability, potency, and viscosity.

The Hammon trials also improved field-based capabilities for testing, again by developing important invisible infrastructure against which field tests could be evaluated. This was achieved at significant fixed cost through careful standardised trial designs, establishing critical viral infection doses, and developing various shared indices to measure qualities such as immunity and degrees of severity in symptoms.

In terms of visible infrastructure, the Foundation strengthened its administrative capacity for coping with the logistics of large-scale immunisation and co-ordinating the supply of testing resources. It was important to ensure there would be volunteers to test on, γ -globulin to test with, and venues for immunisation (e.g. schools). Officials from health departments across the country and over 50,000

such public medals, Sabin was lauded by fellow scientists, elected to the National Academy of Sciences and embraced by virologists worldwide.

teachers provided local knowledge and support when the Foundation needed to navigate through the sensitive issue of using placebos in the trials for the first time.

When a strong imperative to develop a thermostable poliomyelitis vaccine for the eradication effort emerged, it was not pursued successfully because the surrounding infrastructure and other technical systems had moved on. The need for cold chain systems would still remain due to the use of other vaccines that depended on refrigeration did not help. Moreover, new vaccine vial monitoring technologies reinforced the cold chain technological paradigm. Between 1950 and 1991, developing a thermostable vaccine had gone from being impossible to feasible to difficult. If a nascent trajectory becomes locked out by its surrounding technical system, it is not due to any inherent logic of the system, it is because the choice was made too late, after the window for making it had expired.

4.4 Conclusions and policy implications

The paper examined clinical trials as a strategic research site that has hitherto been relatively unexplored. Analysing vaccine development using testing regimes brings into focus different features of medical innovation. The case study has offered evidence for the two main claims of the paper. Firstly, clinical trials are not simply a verification tool; they are part of a learning process that is highly management intensive. This suggests there is a role for clinical research in medical innovation that extends well beyond regulating safety and efficacy. Secondly, multiple trajectories of product development can lead to different kinds of vaccine, each with attributes appropriate for different contexts. This suggests that product development must go hand-in-hand with product choice.

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